straight, the patient can see distant objects and read fine print distinctly. The patient has been under observation for one and a half years and the eyes remain straight, vision being 10 per cent. better than at first. Another case was that of a girl aged 2½ years: V. = 5/200; internal squint in both eyes, very high degree. Atropin was used for two weeks and the following correction gave perfect results: Right eye, + 4.50 V. = 20/20; left eye, + 7.50 V. = 20/20. Both eyes being perfectly straight with glasses on, I ordered full correction to be worn constantly. This case has been under observation for nearly two years and the eyes are straight with the glasses; they converge slightly without the glasses on.

Dr. Edward Jackson, Denver: John Fiske, in his "Myths and Myth-Makers," has written beautifully about the tendency of primitive peoples to find a spirit or indwelling force in all sorts of annoying things. When a man has been killed by a knife, in certain savage tribes, the tribesmen hold an inquest and sentence that knife. Now I think we have something of a survival of that in such phraseology as "innocent, or sinning muscle." Ideas which do not depend on any logical reasoning but are largely a suggestion of the phraseology we use are the chief obstacle to a clear general understanding of this matter of ocular movements and their correction.

TINCTURE OF STROPHANTHUS AND STROPHANTHIN *

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The pharmacology of strophanthus indicates that it has certain advantages over digitalis, and careful clinical observation has sustained the view of pharmacologists that it has a distinct field of usefulness. It is a fact, however, that the average practitioner either refuses to employ strophanthus at all, or, after a brief trial, dismisses it and returns to digitalis.

We believe that the reasons for this state of affairs can be explained satisfactorily, and that the chief causes militating against the proper use of strophanthus can be removed.

One of the principal causes of the disrepute into which strophanthus fell was the utter unreliability of the tincture because of extreme variability in the strength of the seed, according to the testimony of several German investigators. It has been shown[1] that the tincture of strophanthus made by the large manufacturing houses of the United States is surprisingly uniform in potency—much more nearly uniform than is the tincture of digitalis—but American physicians are so impressed with the weight of German opinion that it is difficult to eradicate a false impression of this nature, and particularly since our friends in Germany are still reiterating the statement that tincture of strophanthus is extraordinarily variable and unreliable, though the standardized tincture is now sold there. Inasmuch as this supposed variability does not exist here, we may dismiss that phase of the difficulty.

Another serious disadvantage common to strophanthus and digitalis has been the want of a pure soluble active principle suitable for hypodermic use. This want, at least to the extent of the pure and active principle, has been supplied in the crystallized strophanthin of Thoms.

In this connection it may be said that there is the utmost confusion in the minds of many physicians concerning the different strophanthins, and this is not surprising when even the National Standard Dispensatory gives Thoms' formula under the official strophanthin, quoting Thoms as authority. It is probable that the crystallized strophanthin is the only absolutely pure strophanthin obtainable in commerce, but the American house of the manufacturers was unable to supply this direct, but had to import it to our order. They were unable to tell us, before writing to Germany, whether the strophanthin ordinarily supplied is made by the process of Thoms. Though the official strophanthin is not an absolutely pure product, we wish to state distinctly that we do not pretend to say that it may not answer every purpose for which the crystallized strophanthin is used.

A third, and perhaps the most serious, cause of the disfavor into which strophanthus has fallen is the utter confusion concerning the dose. This naturally follows the conflicting statements regarding the toxicity of the different preparations, since the dose is sharply limited by the toxicity.

Potent remedies are almost universally recommended in minimum doses, and in strophanthin we have at once an exceedingly toxic or a comparatively mild remedy dependent on the mode of administration. Less than a milligram of crystallized strophanthin injected into a vein or subcutaneously may give rise to serious symptoms, while 150 milligrams have been given to a man by the mouth in the course of two days.

Table 1 illustrates the confusion existing regarding dosage. The figures in italics are quoted from the several authorities, the others are equivalents calculated from our comparisons of toxicity; while these equivalents are not exact, we have every reason to believe that the limits of error are very narrow. In general, 200 parts of tincture equal in toxicity one part of crystallized strophanthin, or about two parts of Merck's or Boehringer's.

Table 2 affords a comparison of the toxicity according to different investigators, and it will serve to explain the confusion regarding dosage. Digitoxin has been introduced into the table merely for the sake of comparison. It will be observed that ouabain and crystallized strophanthin, which are identical, have been found by several observers to possess the same ratio of toxicity when compared with other substances.

None of the authorities quoted has compared the toxicity of the official and the crystallized strophanthins with digitoxin on the same animal by the same mode of administration. Gley[2] found crystallized strophanthin, or ouabain (which is identical with the crystallized strophanthin) to be twice as toxic as the common strophanthin (and this agrees very well with our own results on mammals and those of Faust[3]), and eighty times as toxic as digitoxin, as determined by Koppe.

We found the toxicity of crystallized strophanthin for the guinea-pig to be about three times as great as that of digitoxin as determined by Reed and Vanderkleed.[4] Fraenkel[5] found digitoxin to be more than twice as toxic as crystallized strophanthin for the cat by sub-

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* Read in the Section on Pharmacology and Therapeutics of the American Medical Association, at the Fifty-ninth Annual Session, held at Chicago, June, 1908.

[1] The Journal A. M. A., 1907, xlviii, 1177.

[2] Compt. rend. Acad. sc., Paris, cvii, 348.

[3] Arch. Exper. Path. and Pharmacol., xlviii, 272.

[4] Am. Jour. Pharm., lxxx, 110.

[5] Arch. Exper. Path. and Pharmacol., li, 84.

cutaneous injection. We are compelled to reject Fraenkel's results altogether. In addition to an apparent typographical error in his article which has misled others, his conclusions do not bear scrutiny, for a careful examination of his protocols shows that the doses he used were not those stated in the conclusions. Attention is called to the fact because Fraenkel's work has been widely accepted.

Schulz[6] gives the same toxic dose for the dog and rabbit and finds no essential difference in the toxicity of crystallized and amorphous strophanthins. Both these statements are wholly at variance with the results of our numerous experiments and those just quoted.

Hochheim[7] finds, as the result of a few experiments on the rabbit, that crystallized strophanthin is "enormously toxic by vein." We have been unable to kill a rabbit with a dose nearly so small as that which he found fatal, while the dose by the stomach which we found effective is much smaller than that given by him, and whereas he found the crystallized strophanthin about 200 times as toxic by subcutaneous injection as by stomach we were able to obtain a ratio for the rabbit not very much greater than that for the cat and dog under certain conditions, and only about one-eighth as great as that of Hochheim. In no case did we observe as great a degree of tolerance for strophanthin by the mouth in the rabbit as that found by Maurel[8] and Hochheim.

TABLE 1.—THERAPEUTIC DOSES ADVISED BY DIFFERENT AUTHORITIES EXPRESSED IN MILLIGRAMS IN ITALICS, WITH THE CALCULATED EQUIVALENTS IN ROMAN TYPE

Authority.	Crystallized Strophanthus.	U. S. P. Strophanthus.	Tincture.
U. S. P.	0.15	*0.3*	30
U. S. P.	2.5	5.0	*500*
National Standard Dispensary.	0.1-0.15	*0.2-0.3*	20-30
National Standard Dispensary.	1.5-5.0	3.0-10.0	*300-1000*
Mercks' Index[9]	*5x6* daily	10x6 daily	1000x6 daily
Mercks' Index.	0.1-0.5	*0.2-1.0*	20-100
Mercks' Index.	1.5-5.0	3.0-10.0	*300-1000*
Schedel[12]	*5.0-10.0x3* daily	10.0-20.0x3 daily	1000-2000x3 daily
Hochheim.	*5.0x6* daily	10.0x6 daily	1000x6 daily
Kobert[13].	*"preceding too high"*		
Fraenkel[14] (vein).	0.38-0.5	*0.75-1.0*	(unsuited)
Focke[15]	1.5x2 2.1x1 daily	3.0x2 4.2x1 daily	*300x2** *420x1* daily
Bellevue Hospital	3.0-5x6	6.0-10.0x6	*600-1000x6*

* Focke used 5 drops twice, or 7 drops once, a day.

Ratio of toxicity of the smallest single dose advised by mouth (0.2 mg. of the official) to the highest dose given in a day (75 mgs. of the crystallized) = 1 to 750.

We shall see that the tables of toxicity for strophanthin by the mouth are of but little importance unless we know the conditions under which the poison is given.

TABLE 2.—FATAL DOSES IN MGS. PER KG.

	Cryst. Stand.	U. S. P. Stand.	Digitoxin.	Ratios.
Rabbit, st. (M'l.)	....	40.0	....	......
Rabbit, st. (H'm.)	18.0-30.0	....	....	......
Rabbit, s.c. (S'z.)	0.1-0.2	(0.1-0.2)	....	1 :1 :—
Rabbit, s.c. (H'm.)	0.176	....	....	......
Rabbit, s.c. (M'l.)	....	0.4	....	......
Rabbit, v. (M'l.)	....	0.3	....	......
Rabbit, v. (H'm.)	0.128	....	....	......
Dog, st. (S'z.)	2.0	(2.0)	....	1 :1 :—
Dog, s.c. (S'z.)	0.1-0.2	(0.1-0.2)	....	1 :1 :—
Cat, s.c. (F'l)	0.2 (ther.)	....	0.08	1 :— :3
G. P., s.c. (R. & V.)	....	....	1.0	......
—Mgs. to produce systolic standstill in frog.—				
Gley	0.013	0.025	....	2 :1 :—
Fraenkel	....	0.05	0.18	— :4 :1

Faust: Ouabain twice as toxic as glaber-strophanthin.

Haynes: Tincture strophanthus 40 times as toxic as tincture digitalis.

Haynes'[9] conclusions are wholly erroneous so far as the administration of strophanthus by the mouth is concerned. He used massive doses on the cat by the stomach. Rapid absorption occurred, with destruction of only a comparatively small amount, leading to incorrect conclusions.

This want of agreement in the toxicity of strophanthin for different animals would be of much less importance were it not for the fact that these different observers have based the therapeutic dose for man on these results without regard for the conditions which modify their results.

In attempting to find a rational basis for the dosage of different preparations of strophanthus we first determined the toxicity of the tincture, and of the official and the crystallized strophanthins, for different animals by different modes of administration, for, as previously stated, the therapeutic dose must be limited by the toxicity of a given preparation by a given method of administration.

A summary of the results of a large number of experiments is given in Table 3. The most striking fact which this table suggests is the extraordinary discrepancy between the dose of the official strophanthin, on the one hand, and of the tincture and the crystallized strophanthin on the other, if we accept toxicity as a guide to the dose. Thus while the doses of strophanthin and of the tincture given by the U. S. P. indicate that official strophanthin is 1,600 times as active as the tincture, we find that it is only about 100 times as active when given under similar conditions.

TABLE 3.—FATAL DOSES IN MGS. PER KG. (H. & B.)

Animal.	Cryst. Stroph.	U. S. P. Stroph.	Tincture.
Cat, m't'h.	1.0-2.0	4.0-6.0	65-1000
Dog, m't'h.	1.5	4.0-5.0	?-500-1000
Rab., m't'h.	10.0	25.0	......
Cat subcut.	0.15	0.35	40
Dog, subcut.	0.15	0.35	40
Rab., subcut.	0.35	0.8	125
Guinea-pig, subcut.	0.3	....	...
Cat, vein.	0.1	0.25	35
Dog vein	0.125	0.27	36

TINCTURE TO DOG

Tongue, 200; emesis.
Rectum, 200; def'n.
Large intestine, 30; none in 1-½ hrs.
Jejunum, 446; toxic in 55 minutes.
Ileum, 500; died in 1 hr.
Duodenum, 600; none in 1-½ hrs.
Duodenum, 1,000; died in 38 minutes.
Duodenum, 600; died in 45 minutes.
Rectum, cryst. stroph., 1 mg. per kg.; none.

The crystallized strophanthin is advised in doses from five to fifteen times as large as those of the official strophanthin, but the table seems to indicate that the amount of the official product to be given by the mouth should be twice that of the crystallized, or from ten to thirty or even fifty times that commonly advised. We can not state with sufficient emphasis that we are not prepared to advise that the dose be increased to that extent in the

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6. Viertljschr. f. gerichtl. Med., xxi, 293.
7. Centralbl. f. inn. Med., xxvii, 65.
8. Soc. de biol., 1901, p. 837.
9. Bio-chem. Jour., 1906, i, 62.
12. Ber. d. deutsch. pharm. Gesellsch., xiv, 120.
13. Lehrbuch der Intox., ii, 1215.
14. Arch. Exper. Path. and Pharmacol., lvii, 79.
15. Therap. d. Gegenw., 1906, viii, 348.

present state of our want of knowledge, but we do say that the evidence shows the need of careful clinical investigation of the question.

The ratio of toxicity is fairly well maintained for the two strophanthins for different animals with different modes of administration, but it is possible that the very soluble amorphous strophanthin may, under certain conditions, show a different rate of absorption from the human alimentary canal from that shown by the lower animals and may, therefore, show an extraordinary toxicity for man when given by the mouth.

When large doses of tincture of strophanthus, or the crystallized strophanthin, are given to man by the mouth, nausea, vomiting and even bloody diarrhea ensue. This prevents the further absorption of the poison and explains why death practically never results from very large doses of these substances when they have been given in this way.

The experience of Fraenkel[10] and others indicates that the dose of the official strophanthin by vein is about one milligram. This is given at once and is not repeated within twenty-four hours. Table 3 indicates that about 0.4 mg. of crystallized strophanthin is equivalent to 1 mg. of the official drug by the vein.

Hochheim,[7] in Unverricht's clinic, advised 5 mgs. of the crystallized strophanthin as the dose by the mouth, or 30 mgs. in this way as the maximum daily dose. Kobert thinks this dose is too high, basing his opinion on his own experiments on animals. The toxic equivalent of this dose seems to show that the single adult dose of the official strophanthin by the mouth should be about 10 mgs. and the full daily dose 50 or 60 mgs., but should this amount be absorbed quickly it would surely prove fatal. As previously stated, 150 mgs. of the crystallized drug, the equivalent of more than 300 mgs. of the official drug, have been given (by Hochheim) to a patient by the mouth in the course of two days; it caused vomiting and bloody diarrhea.

The amounts given in Table 3 are suggested as the basis of a rational clinical observation and not with any idea that it is the last word on the subject of dosage.

We believe that the strophanthins of Merck and of Boehringer & Sons and probably those of other makers are fairly uniform, but they are not absolutely pure crystalline bodies, and we are unable to vouch for them. Several samples of Merck's and Boehringer's strophanthin purchased at intervals of a year or more were examined and no difference in activity could be observed. So long as the crude drug can not be identified with certainty and is said to be the subject of gross adulteration, while the different strophanthins differ markedly in toxicity (or, what amounts to the same thing, in purity), it would seem that prudence demands that the manufacturers should standardize the non-crystalline strophanthins by a given method of standardization. For this purpose we would recommend that the amount required to kill a kg. of healthy normal cat within an hour, when a 1/10,000 solution in normal saline is injected at once into the femoral vein, should be taken as the unit and called one cat unit. This amount corresponds very nearly to 0.1 mg. of the crystallized drug.

The crystallized strophanthin obtained by the process of Thoms from *Strophanthus gratus* has a definite melting point and well defined solubilities. It is said to be soluble in 30 parts of absolute alcohol and in 100 parts of water. The following observation, which was not investigated farther, is of interest in view of the fact that an alcoholic stock solution might be ordered. One part of crystallized strophanthin dropped into alcohol formed a pasty mass which dissolved only after warming, and on standing a few days it crystallized out on the sides of the bottle. The solution made of the powdered drug was permanent. The crystals shaken with so-called absolute alcohol (about 99 per cent.) for several days did not dissolve in the proportion of 1 to 100.

It would not be profitable to discuss all of our experiments in detail, but certain significant results will be considered. The cat and dog show a nearly identical degree of susceptibility, the latter being a trifle more resistant. Both of these animals vomit with such uniformity so soon as a toxic dose of strophanthin enters the circulation that it is difficult to fix the fatal dose by the mouth with any degree of precision.

In order to obviate this difficulty the effort was made to depress the vomiting center by a small dose of the tincture which was followed by a larger amount. This was wholly unsuccessful, as the animals promptly vomited as soon as a toxic dose had passed into the circulation. Morphin was then employed to depress the vomiting center of another dog, and the dose of strophanthus which would produce only vomiting under normal conditions then promptly caused death. The importance of this in therapeutics under certain conditions is obvious. In this way it was found that the single fatal dose of the tincture for the dog by mouth is about 600 to 1,000 mgs. per kg., when the tincture is well diluted with water.

A form of dilution favorable for quick absorption was then tried; the concentrated tincture or alcoholic solution of strophanthin was washed down in a little alcohol, and in this way we were able to kill or severely poison several animals with doses but little above those required by subcutaneous injection and very much less than those usually required to cause death after oral administration.

Sixty-six milligrams of the tincture per kg. proved fatal to Cat M when given in this way. A proportionate amount may be taken in the course of a day by a man in the usual way and give rise to no symptoms whatever. The cat used in this experiment was somewhat emaciated and the result was not considered wholly satisfactory on that account, but prompt emesis followed this dose given in the same way to Cats 3 and 4, and emesis occurred repeatedly in Cat 4. This shows that the amount absorbed was not very far from the fatal dose and might well have proved fatal had emesis not followed. Furthermore, it may be stated in support of the result with Cat M that a sick rabbit was repeatedly injected with large doses of strophanthus and only succumbed to a dose which would prove fatal to a normal rabbit.

EXPERIMENT 1.—March 24, 1908: Cat M., male, weight 1.1 kg., has been the subject of a number of experiments and is very much emaciated. Had been used for strophanthus one week previously. 3:15 p. m.: 0.066 c.c. tincture strophanthus per kg., diluted with a little alcohol, washed down with 1 c.c. alcohol, 5:45 p. m.: Cat lies down, but is able to get about.

March 25: Cat found dead.

The rabbit is somewhat more tolerant than the cat or dog when the drug is injected subcutaneously, and very much more so when it is given by the mouth. The white rat is extraordinarily tolerant whether the poison be given by the mouth or subcutaneously; thus the equivalent of 70 mgs. per kg. of crystallized strophanthin was injected subcutaneously in one case without producing any perceptible effect, while another white rat weighing only 156 gms. ate 100 mgs. with his food without ill effects.

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[10] Arch. Exper. Path. and Pharmacol., lvii, p. 79.

Disintoxication appears to be more rapid in the case of the rodents than with the cat and dog, for the rat was seen to return to the poisoned food after brief periods of depression, and the rabbits ate with avidity in a few hours after a nearly fatal dose by subcutaneous injection, while the effects of large doses were observable for several days in the cat and dog.

The difference in toxicity seen after slow and rapid absorption seemed to support the explanation of von den Velden[11] that the lesser toxicity of the digitalis bodies by the mouth is due to a slower absorption. That this does not suffice to explain the differences seen with strophanthin is shown by the results of experiments 2, 3, 4 and 5. In experiments 2 and 3 a very dilute solution of the crystallized strophanthin (1:250,000) was slowly injected into the femoral vein; although free diuresis resulted from the injection of such a large amount of normal saline, the fatal dose of strophanthin was but little more than that which the animal survived for more than two hours in experiment 4, in which the solution, 1:10,000, was injected at once into the vein, and the single dose given in experiment 2 was the same as that which proved fatal with slow injection in experiment 4, but this is explained in part by the excess of fat.

If by "slower absorption" von den Velden would have us understand the failure to absorb the greater portion of a dose during its passage of the entire small intestine, then his explanation must be accepted as probably correct. This is failure to absorb, rather slow absorption, in the usual acceptation of the expression.

Experiment 2.—April 18, 1908: Dog 4, male mongrel, weight 14.85 kg., excessively fat.

10 a. m.: 0.01 gm. morphin sulphate per kg. subcutaneously.

10:15 a. m.: Light ether anesthesia. Cannula into femoral vein.

10:18 a. m.: Ether withdrawn.

10:42 a. m. to 12:05 p. m.: 1/800 mg. per kg. per minute of crystallized strophanthin in normal saline (1:250,000) injected into vein.

12:05 p. m.: Injection stopped, and dog died in about fifteen minutes.

Total dose: 1.58 mg. or 0.105 mg. per kg.

Total normal saline: 400 c.c. or 27 c.c. per kg.

Experiment 3.—April 18, 1908: Dog 5, male, good condition, weight 7.4 kg.

2:05 p. m.: 0.01 gm. morphin per kg.

2:15: Ether, light anesthesia. Cannula into femoral vein.

2:30 to 5:13 p. m.: Injection as in Experiment 2 till death of animal.

Total dose: 1.3 mg. or 0.175 mg. per kg. crystallized strophanthin.

Total normal saline: 325 c.c. or 44 c.c. per kg.

Time of injection: 2 hours 43 minutes.

Experiment 4.—April 20, 1908: Dog 6, fox terrier, fine condition, weight 8.5 kg.

1:10 p. m.: 0.01 morphin sulphate per kg. subcutaneously. Ether as in Experiment 2. Cannula into femoral vein.

1:38 p. m.: 0.1 mg. crystallized strophanthin per kg. into vein.

3:48 p. m.: 0.025 mg. per kg. as before.

4:01 p. m.: Animal died.

Total dose: 0.125 mg. per kg. in 10,000 parts normal saline.

Experiment 5.—April 24, 1908: Dog 8, female, mongrel, weight 7.65 kg.

11:25 a. m.: 0.01 gm. morphin sulphate subcutaneously. Ether for light anesthesia. Cannula into femoral vein.

12:07 to 12:42 p. m.: 100 c.c. (1:100,000) strophanthin (1 mg.).

12:57 to 1:07: 10 c.c. (1:100,000) strophanthin (1/10 mg.).

1:22 to 1:29 p. m.: 10 c.c. (1:100,000 strophanthin, (1/10 mg.).

1:44 to 1:49 p. m.: 5 c.c. (1:100,000) strophanthin (1/20 mg.).

2:14 to 3:10 p. m.: 58 c.c. (1:100,000) strophanthin (58/100 mg.).

3:14 to 3:25 p. m.: 18 c.c. (1:100,000) strophanthin (18/100 mg.).

4 to 4:49 p. m.: 45 c.c. (1:100,000) strophanthin (45/100 mg.).

4:49 p. m.: Dog died.

Total duration of injection: 4 hours 42 minutes.

Total dose: 246 c.c., 2.46 mg. strophanthin.

Dose per kg.: + 2.46 — 7.65 = 0.322 mg.

This method always gives results somewhat too high, and if 20 per cent. of the lethal dose is destroyed in the time of the experiment it gives 0.27 mg. per kg. This is almost the exact fatal dose by vein when given at once.

This is also shown in the case of the official strophanthin. In experiment 5 a dog received 0.322 mg. of official strophanthin by the vein in the course of nearly five hours. Since the animal organism is capable of destroying almost the full lethal dose in twenty-four hours, we should expect the effective dose in this case to be at least 20 per cent. higher than when the injection is made at once. This would indicate that 0.27 mg. is the fatal dose of strophanthin by the vein for the dog. This is almost precisely the effective dose when given at once by the vein.

Curarin and antiarin are said to be destroyed in the liver, and this source of destruction of strophanthin, of course, presented itself to our minds. That the liver does not destroy strophanthin in amounts sufficient to account for the lessened toxicity by the mouth is shown by comparing the results of experiments 3 and 6. A dilute solution is just as toxic when injected slowly into the splenic vein as when it is injected into the femoral. In fact, the animal which received the injection into the splenic vein succumbed to a slightly smaller dose, but the difference lies wholly within the limits of ordinary variation.

Experiment 6.—Female fox terrier, quite fat, weight 10.35 kg.

10:25 a. m.: 0.01 gm. morphin sulphate per kg. subcutaneously.

10:45 a. m.: Light ether anesthesia. Cannulas into carotid artery and splenic vein.

11:34 a. m. to 1:54 p. m.: Injection as in Experiment 3 of crystallized strophanthin, 1 to 250,000 normal saline.

1:57 p. m.: Animal died.

Total dose: 1.52 mg. or 0.147 mg. per kg.

Time of injection: 2 hours 29 minutes.

Peptic and activated pancreatic digestants, as well as bile, were found to exert only an unimportant influence on the toxicity.

When a large dose of strophanthin was injected directly into the duodenum an amount equal to ten times the fatal dose by vein disappeared from the lumen of the small intestine in the course of an hour and a half without causing toxic symptoms in the dog, while the solution remaining unabsorbed in the small intestine retained its toxicity, as shown by injecting it into a cat subcutaneously. The cat promptly died with typical symptoms.

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[11] München. med. Wchnschr., liii, 2137.

From this it appears probable that strophanthin is destroyed in part in the intestinal canal when the drug is taken by the mouth, but that rapid absorption may take place is shown by the results of experiments already quoted, and by one in which a large amount was introduced directly into the duodenum and death with typical symptoms followed in thirty-eight minutes.

While one of us (R. A. H.) has concerned himself chiefly with the questions of dosage and the factors which modify this with different methods of administration, the other (H. C. B.) has made a number of clinical observations on patients in Bellevue Hospital. The results of these observations will be the subject of a subsequent communication, but the point to which we now wish to draw attention is the subcutaneous injection of strophanthin.

Dr. Bailey employed the official strophanthin, dissolved in sterile salt solution, in one case, but for the most part the crystallized strophanthin was used. This was dissolved in 4,000 parts of salt solution, which was then sterilized by boiling, and the appropriate dose—0.3 to 0.5 mg.—was put into sterile serum tubes and the latter sealed in the flame. This solution was injected deeply into the gluteal muscle once in twenty-four hours. It gave rise to a slight degree of pain lasting about an hour, which was never sufficient to prove a serious objection to its use in this way. No side actions, such as described by Fraenkel, were seen in any case. The action was more prompt than could be elicited by 1 c.c. of the tincture given by the mouth every four hours—6 c.c. in the twenty-four hours.

CONCLUSIONS

The dosage and the proper mode of exhibiting strophanthus and strophanthin require clinical investigation. The action of strophanthin may be elicited promptly in suitable cases by injecting it subcutaneously. Three-tenths to half a milligram of the crystallized strophanthin in sterile (boiled) salt solution, 1/4000, may be injected deeply into the gluteal muscle once in twenty-four hours without fear of abscess formation or other side actions.

The single adult dose of crystallized strophanthin by the mouth is about 5 mgs. or less, the daily dose 30 mgs. or less. The single adult dose of the official strophanthin by the mouth is probably about 10 mgs., and the daily adult dose by the mouth is probably about 60 mgs., but the latter dose should not be used until we have further clinical experience concerning the various factors governing its absorption.

The action of tincture of strophanthus by the mouth and the factors modifying its absorption require further clinical study. Uniformity of action can only be secured by uniform absorption, and this is influenced by the menstruum in which the drug is given and the condition of the alimentary canal at the time of administration.

It is quite possible that diet may influence the absorption of strophanthin in the human alimentary canal, so that man may at one time resemble the rodent and at another time the carnivorous animals (cat and dog) in susceptibility to strophanthin.

ABSTRACT OF DISCUSSION

DR. TORALD SOLLMANN, Cleveland, Ohio: This paper explains why strophanthus has not received the popularity to which one might suppose it entitled. I think that clinicians have been extraordinarily wise in not relying on a drug about which so little is really known. Yet strophanthus contains great capacities for good and it is to be hoped that investigations such as Dr. Hatcher's will be carried still further. These investigations tend to substitute definite for indefinite knowledge. The dose now varies anywhere from 1 to 1,000. I believe that if these investigations are continued, strophanthus will prove to be a very important drug.

DR. C. W. EDMUNDS, Ann Arbor, Mich.: The report of the uniformity of strophanthus tinctures did not agree with the results I obtained last year. I found that strophanthus tinctures varied exactly the same amount that the tinctures of digitalis varied; that is, the fatal dose in one preparation was 0.0012 of a cubic centimeter, in another 0.0025, in another 0.005, in other words a ratio of 1 to 4. In regard to the difference in toxicity between tincture of digitalis and strophanthus, the results I obtained with tincture of strophanthus, taking the average of all the preparations studied, showed that strophanthus was about sixty-seven times as toxic as digitalis, which agreed fairly well with Haynes' results. He compared 2.5 per cent. tincture of the British Pharmacopeia with a 12.5 per cent. digitalis tincture. I forget his exact figures, but I think he found a ratio in toxicity of about 12 to 1, which, multiplied by 5 on account of the difference in strengths of the two tinctures, would make his figures agree pretty closely with mine.

MR. M. I. WILBERT, Philadelphia: The figures mentioned by Dr. Edmunds a few moments ago are further emphasized by the suggestions of Dr. Hatcher on the variability of the sources of strophanthus. The drug strophanthus has been before the medical public for upward of forty years, and has received ample recognition in the voluminous literature that has been published since 1873, when Dr. Frazer read his first paper on this drug. It is evident that the majority of medical men do not feel safe in using strophanthus. This feeling of uncertainty, evidenced by the fluctuating use of strophanthus, is, no doubt, largely due to the irregularity in the source of the seed. The Pharmacopeia gives *Strophanthus kombé* as the only source of drug from which the official tincture of strophanthus can be made. As a matter of fact, *Strophanthus kombé* was, for a number of years, practically out of the market. The annual reports of European drug houses have repeatedly called attention to the fact that the supply of *Strophanthus kombé* was meager and that the available drug was frequently mixed with other, more or less inert, seeds. In a recent paper by Professor Gilg, read before the Pharmaceutical Society in Germany, he suggests that *Strophanthus hispidus* be made the official source. *Strophanthus hispidus* is cultivated in a number of places in South Africa, is readily controlled and always comes into the market of uniform quality. We have reason to believe that *Strophanthus gratus* is the source of crystalline strophanthin, which, as Dr. Hatcher has pointed out, is identical with ouabain, a glucosidal substance obtained from the wood of a species of Acocanthaceæ, and is at least twice as strong as the official strophanthin. Here is a possible complication that should be guarded against. I think it would be unfortunate indeed if *Strophanthus gratus* should be generally confounded with the official strophanthus. In addition to this complication with the seed we may also have the same complication in connection with the active principles. At the international conference held in Brussels in 1902 for the unification of the formulas for potent medicaments, the delegates present were so uncertain about the origin of strophanthus that the committee did not include the origin or the description of the seed in the final protocol, despite the fact that it did include the tincture. The proposed international tincture of strophanthus differs from the U. S. P. tincture in the strength of alcohol to be used in the percolation of the drug and that is another point which may be of importance. The international tincture is more readily made, the drug is more thoroughly exhausted, and the finished preparation stands up better and remains clearer longer than the corresponding U. S. P. preparation. The international menstruum represents 75 per cent. alcohol, while the menstruum directed in the United States Pharmacopeia represents about 65 per cent. of alcohol.

Dr. E. M. Houghton, Detroit: I am particularly glad to note that Dr. Hatcher's statements relative to the toxicity of strophanthus coincide almost exactly with those I made in a paper before this section ("The Pharmacologic Assay of the Heart Tonics," The Journal, Oct. 22, 1898), I think exactly ten years ago. I pointed out that the toxic dose of the strophanthins on the market varied from 1 to 90; in other words I found with different samples of strophanthin obtained in this country and Europe one strophanthin ninety times as strong as another. At the same time I called attention to the variability in the activity of tincture of strophanthus and preparations of digitalis, and proposed a method of determining the activity of the heart tonics and especially of the tincture of strophanthus. I used as a standard 0.00015 c.c. tincture of strophanthus per gram body weight of frog as the minimum fatal dose when injected into the abdominal lymph sac.

Since then it has been my privilege to examine or have examined hundreds of samples of tincture of strophanthus, and I have adhered to that standard. I have in course of preparation just now a paper on the heart tonics, in which I shall enter more fully into the question of standards for digitalis and strophanthus. I have found the tincture of strophanthus prepared according to the seventh revision of the U. S. P. approximately ten times as active as the corresponding fluidextract of digitalis. In other words, the standard I have adopted for 5 per cent. tincture of strophanthus, 0.00015 c.c. per gram body weight of frog, is exactly one-tenth that for fluidextract of digitalis (0.0015 c.c.), when similarly injected.

Examination of these figures shows that strophanthus is two hundred times as active as digitalis, in terms of crude drug. It seems to me from the very large number of samples examined of different preparations of these two drugs that the figures just cited as standards for their strength are reasonable as representing the activity of average samples of first-class drug.

Dr. Robert A. Hatcher, New York: The difference in toxicity of strophanthus and digitalis is largely based on the length of time required. It is well known that digitoxin reacts slowly. It will probably take two hundred times as much digitoxin as of strophanthin to kill in an hour, but if you take the minimum fatal dose, regardless of time, the difference is much less. Fraenkel found that the minimum fatal dose of digitoxin did not kill within eight days (cat). An enormous dose is required to kill within an hour, whereas ouabain is quickly fatal in minimum fatal doses. That is probably why Hedbom, experimenting on frogs, found ouabain eighty times as toxic as digitoxin. As to variability of the tincture, I do not deny that it may exist, but there is no excuse for any one's failure to obtain reliable preparations, and we can obtain reliable preparations of strophanthus without limiting ourselves to those of one manufacturer. I compared the tincture made by Burroughs, Wellcome & Co. with those of Parke, Davis & Co. and Squibb, and with those made from seed obtained from Gilpin, Langdon & Co. and one from a specimen of seed that had been in our laboratory for nearly twenty years, and all were found to be of practically the same strength. Samples were purchased of the east side drug stores in New York and the better class of stores were purposely avoided. There is no reason why the crystalline strophanthin should be confused with the official, but the difference in toxicity has not been sufficiently emphasized. Ouabain is the most toxic; strophanthin, which is methyl ouabain, is about one-half as toxic, and acocantherin, which is dimethyl ouabain, is about one-fourth as toxic; this is very suggestive as to the effect of methyl groups on the toxicity. There is absolutely no reason why crystalline strophanthin should not be prescribed. I believe that Dr. Edmunds must have used much larger doses of digitoxin than the minimum fatal. There is certainly no such difference in the toxicity of strophanthus and digitalis as suggested, for no one could use 3,000 (50 × 60) minims of tincture of digitalis daily without effect. Haynes states that strophanthus given by the mouth is fifty times as toxic as is digitalis, but that is absolutely untrue, at least under ordinary conditions.

DEPARTMENTS OF HYGIENE UNDER BOARDS OF EDUCATION *

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In the modern scientific business life the technical business expert has a permanent place. The erection of a city structure involves the cooperation of engineering and architectural experts as never before. Electric and mining work involves groups of experts, each connected with some special phase of the subject. School boards have had new problems thrust on them, and the employment of business agents and building experts has become indispensable. It is my belief that the group of problems centering about the health of school children demands technical treatment as highly specialized as that required for other departments. A few statements of fact will bring out the necessity of the measure here advocated.

On good eyesight depends to a large degree one's ability to conduct successfully the affairs of life. Notwithstanding the great damage or degeneration that the vision of American school children is constantly undergoing, there is hardly a school board in America that has in its employ a technical expert to decide on questions relating to eyesight. School-books are adopted, but no standards have been established based on adequate research as to the length of lines for the various ages, size of type, size and stroke of letter in connection with the lines, the width of the margins, the use of halftones as compared with outline drawings, the use of dead-finished as compared with coated paper, and similar questions. There are authorities on many of these matters, but we have no experts in the employ of departments of education who can speak authoritatively from the standpoint of special study made of these conditions as they exist in American schools.

This extraordinary condition with reference to the problem of vision does not stand alone. Through the school we have changed the life of the child from one of predominant activity to one predominantly sedentary in character. During five hours of the school day for ten months in the year children are obliged to be seated for the major portion of the time. So extensive a readjustment of the life habits of the young of a species has never before taken place. Its effects on digestion, circulation, nutrition and posture are as yet unknown. Yet there is not employed by any board of education in America one expert to make a special study of this group of problems centering about the changed conditions of life as they exist under the conduct of the modern school.

The returns from examinations made by competent physicians in all parts of America indicate that there are many children in all parts of America whose school progress is hindered and whose prospects in life are lessened by hypertrophied tonsils and adenoids; and yet up to the present time there is not employed by a department of education in America a technical expert to study the reasons for the occurrence of such growths, particularly as related to school life, or the means of prevention. The only thing that is being done is to attempt to operate on the tonsils and adenoids after they have grown.

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* A paper prepared for the Section on Hygiene and Sanitary Science of the American Medical Association, Chicago Session, 1908, but not read.